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| 10/659,083 | 09/09/2003 | Simon Delagrave | 20446-002001 / BTS0001-10 | 2730 |

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| EXAMINER | |
|---|---|
| STEELE, AMBER D | |
| **ART UNIT** | **PAPER NUMBER** |
| 1639 | |
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/659,083 | DELAGRAVE, SIMON | |
| | Examiner | Art Unit | |
| | Amber D. Steele | 1639 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *06 February 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *61-63 and 67-69* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *61-63 and 67-69* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Continued Examination Under 37 CFR 1.114*

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on February 6, 2008 has been entered.

### *Status of the Claims*

2. The amendment to the claims received on June 4, 2007 canceled claims 1-60 and added new claims 61-69.

The amendment to the claims received on February 6, 2008 amended claims 61-63 and canceled claims 64-66.

Claims 61-63 and 67-69 are currently pending and under consideration.

### *Election/Restrictions*

3. Applicant elected, with traverse, Group I (original claims 1-12, now claims 61-63 and 67-69) in the reply filed on April 20, 2006.

### *Priority*

4. The present application claims benefit of U.S. application 60/416,819 filed October 8, 2002.

However, the later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the

later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed application, Application No. 60/416,819, fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. The specification of U.S. provisional application 60/416,819 does not disclose PDZ domains. Therefore, the priority date of the presently filed application is the present filing date of September 9, 2003.

***Invention as Claimed***

5. A method of countering the development of resistance in a parent target to a parent neutralizing agent wherein the parent neutralizing agent neutralizes the parent target and wherein said parent neutralizing agent is a protein comprising a PDZ domain comprising coevolving said parent target and said parent neutralizing agent wherein said coevolving comprises: (a) diversifying said parent target to form a diversified population of next generation targets, (b) selecting one or more next generation targets from said diversified population wherein said selected one or more next generation targets has improved resistance to said parent neutralizing agent, (c) diversifying said parent neutralizing agent to form a diversified population of next generation neutralizing agents, (d) selecting one or more next generation neutralizing agents from said diversified population wherein the selected one or more next generation neutralizing agents has improved neutralizing activity compared with said parent neutralizing agent against said next generation target, (e) optionally repeating said diversifying and selecting using said one to more next generation neutralizing agents or next generation targets wherein the improved

neutralizing activity of the selected next generation neutralizing agent counters the improved resistance of the selected next generation parent target thereby countering the development of resistance and variations thereof.

**Withdrawn Rejections**

6. The rejection of claims 61-64 and 66-69 under 35 U.S.C. 102(b) as being anticipated by Karrer et al. WO01/32712 A2 published May 10, 2001 is withdrawn in view of the claim amendments received on February 6, 2008 (i.e. PDZ domain; in preamble, but provides additional structural information regarding the parent neutralizing agent).

7. The rejection of claims 61-64 and 68 under 35 U.S.C. 102(b) as being anticipated by Rosin et al. PNAS 96: 1369-1374, 1999 is withdrawn in view of the claim amendments received on February 6, 2008 (i.e. PDZ domain; in preamble, but provides additional structural information regarding the parent neutralizing agent).

8. The rejection of claims 61-63 and 67-68 under 35 U.S.C. 102(b) as being anticipated by Eaton et al. U.S. 5,723,289 issued March 3, 1998 is withdrawn in view of the claim amendments received on February 6, 2008 (i.e. PDZ domain; in preamble, but provides additional structural information regarding the parent neutralizing agent).

9. The rejection of claims 61-62 and 64-65 under 35 U.S.C. 102(b) as being anticipated by Staudinger et al. J. Biol. Chem. 272(51): 32019-32024, 1997 is withdrawn in view of the claim amendments received on February 6, 2008.

## New Objection

### *Specification*

10. The disclosure is objected to because of the following informalities: the first line of the specification claims priority to U.S. provisional 60/416,819. However, priority to the provisional application is denied (see priority section above).

Appropriate correction is required.

## New Rejection

### *Claim Rejections - 35 USC § 112*

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims 61-63 and 67-69 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a **written description** rejection.

Claim 71 is drawn to a method of countering the development of resistance in a parent target to a parent neutralizing agent wherein the parent neutralizing agent neutralizes the parent target and wherein said parent neutralizing agent is a protein comprising a PDZ domain comprising coevolving said parent target and said parent neutralizing agent wherein said coevolving comprises: (a) diversifying said parent target to form a diversified population of next generation targets, (b) selecting one or more next generation targets from said diversified

population wherein said selected one or more next generation targets has improved resistance to said parent neutralizing agent, (c) diversifying said parent neutralizing agent to form a diversified population of next generation neutralizing agents, (d) selecting one or more next generation neutralizing agents from said diversified population wherein the selected one or more next generation neutralizing agents has improved neutralizing activity compared with said parent neutralizing agent against said next generation target, (e) optionally repeating said diversifying and selecting using said one to more next generation neutralizing agents or next generation targets wherein the improved neutralizing activity of the selected next generation neutralizing agent counters the improved resistance of the selected next generation parent target thereby countering the development of resistance and variations thereof. The invention as claimed encompasses all known proteins comprising PDZ domains and all potential proteins comprising PDZ domains since virtually any protein can be neutralizing in view of applicant's definition of neutralizing as binding. Furthermore, the invention as claimed encompasses all know and unknown parent targets, parent target mutations, and PDZ domain mutations including those mutation that would delete the PDZ domain. The claimed invention states that the development of resistance must be countered and the process must result in an improved neutralizing activity to a target with improved resistance. The claimed invention does not include any information correlating the PDZ structure to a specific neutralizing function against a specific target.

The specification focuses on neutralizing antibodies (i.e. monoclonal antibody-resistant mutants and RSV as the target; please refer to Examples 1-4), antibiotic resistance (i.e. vancomycin and *S. aureus* as the target; please refer to Example 5), and chemical drugs (i.e. Gleevec® and chronic myeloid leukemia as the target; please refer to Example 6). In addition,

the specification only refers to PDZ domains as a potential alternative to neutralizing antibodies (please refer to page 6, paragraph 23; "Some further examples of interactive pairs include a phosphorylated segment of a protein and an SH3 domain as well as a C-terminus of a polypeptide and a PDZ domain"). Furthermore, the specification does not teach how a PDZ domain is neutralizing to a resistant target. Therefore, one skilled in the relevant art would not reasonably conclude that the Applicants had possession of the invention as claimed since a correlation of the PDZ domain to the function of neutralization of a resistant target is not included in the claimed invention.

See Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was *in possession of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See page 1116.).

With the exception of a method of countering the development of resistance via neutralizing antibodies, antibiotics, or Gleevec® as disclosed by the specification (Examples 1-6), the skilled artisan cannot envision the method of claim 61. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class wherein the specification provided only the bovine sequence.

Thus, the specification does not provide a single embodiment (i.e. single, specific species) of the presently claimed invention (i.e. countering resistance via PDZ domains), a single embodiment of a PDZ domain containing protein that counters resistance, functional characteristics correlating a PDZ domain containing protein to counter resistance in a single target. In addition, the level of skill in the art is such that one would not recognize the necessary attributes correlating every known and unknown PDZ domain comprising protein with the ability to neutralize resistance of every known and unknown target (e.g. a single PDZ domain comprising protein would not be expected to neutralize resistance in viruses, bacteria, cancer, etc., a PDZ domain comprising protein would have to be correlated to disease, a PDZ domain comprising protein would have to be a viable treatment, etc.). This appears to be especially critical considering that applicant's examples have all utilized commercially available treatments for disease (i.e. RSV monoclonal antibody, vancomycin, Gleevec®; see Examples 1-6).

13. Claims 61-63 and 67-69 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This is an **enablement** rejection.

There are many factors to consider when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any experimentation is "undue". These factors include, but are not limited to:

1. The breadth of the claims;

2. The nature of the invention;

3. The state of the prior art;

4. The level of skill in the art;

5. The level of predictability in the art;

6. The amount of direction provided by the inventor;

7. The presence or absence of working examples;

8. The quantity of experimentation necessary needed to make or use the invention based on the disclosure.

See *In re Wands* USPQ 2d 1400 (CAFC 1988):

The breadth of the claims and the nature of the invention:

Although addressing PDZ domain comprising proteins as neutralizing reagents, the genus of PDZ domain comprising proteins is large and applicant has not disclosed a single species of PDZ domain comprising protein that has neutralizing activity. Accordingly, the claims encompass every known and unknown PDZ domain comprising protein and every known, unknown parent target, every known and unknown next generation neutralizing agent (i.e. including agents where the PDZ domain has been deleted), and every known and unknown next generation parent target wherein any diversity (e.g. naturally occurring, selective pressure mutations, random mutagenesis, etc.) is possible. Accordingly, the claim scope is unduly broad with respect to encompassed PDZ domain proteins, parent targets, method of diversifying, next generation neutralizing agent, and next generation parent target.

The state of the prior art and the level of predictability in the art:

While, PDZ domains have been utilized as "markers" in assays for HIV protease activity (see Hamilton et al., A PDZ domain-based assay for measuring HIV protease activity: Assay design considerations, Protein Science 12: 458-467) and methods of coevolution of HIV protease inhibitors are known (see Stoffler et al., Evolutionary Analysis of HIV-1 Protease Inhibitors: Mehtods for Design of Inhibitors that Evade Resistance, Proteins: Structure, Function, and Genetics 48: 63-74, 2002), the art is silent with regard to methods of countering the development of resistance in a parent target to a parent neutralizing agent that is a protein comprising a PDZ domain. Therefore, the level of predictability in the art is unknown.

The level of skill in the art:

The level of skill would be high, most likely at the Ph.D. level.

The amount of direction provided by the inventor and the existence of working examples:

There are no specific examples directed to the presently claimed invention, nor is there any guidance as to how to specifically utilize a PDZ domain comprising protein to counter the development of resistance in a parent target. The teachings in the specification refer to coevolution methods for neutralizing antibodies (i.e. monoclonal antibody-resistant mutants and RSV as the target; please refer to Examples 1-4), antibiotic resistance (i.e. vancomycin and *S. aureus* as the target; please refer to Example 5), and chemical drugs (i.e. Gleevec® and chronic myeloid leukemia as the target; please refer to Example 6). Furthermore, no direction is provided on how to neutralize any possible parent target with any possible PDZ domain comprising protein or to continue on with the method and find improved neutralizing activity of next generation neutralizing agents which counter the improved resistance of the selected next generation parent target.

The quantity of experimentation needed to make or use the invention based on the content of the disclosure:

In light of the unpredictability surrounding the claimed subject matter, the undue breadth of the claimed invention's intended use, and the lack of adequate guidance, one wishing to practice the presently claimed invention would be unable to do so without engaging in undue experimentation. One wishing to practice the presently claimed invention would have to find a PDZ domain comprising protein that is correlated to a disease or can neutralize a target, produce mutants of the target which confer resistance to the target that is specific to the neutralizing activity of the PDZ domain comprising protein, produce mutants of the PDZ domain comprising protein, and screen for improved neutralizing activity that can counter the development of resistance to the improved next generation target without any guidance from the present specification on which PDZ domain comprising proteins, targets, or mutations to start with.

***Conclusion***

14. The art made of record and not relied upon is considered pertinent to applicant's disclosure. Ferrer et al., Directed evolution of PDZ variants to generate high-affinity detection reagents, Protein Engineering Design & Selection 18(4): 165-173, 2005 and Ferrer et al., A PDZ Domain-Based Detection System for Enzymatic Assays, Analytical Biochemistry, 301: 207-216, 2002.

***Future Communications***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amber D. Steele whose telephone number is 571-272-5538. The examiner can normally be reached on Monday through Friday 9:00AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Amber D. Steele/
Patent Examiner, Art Unit 1639

April 25, 2008